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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/558,149	04/26/2000	Nicholas Nicolaides	01107.00004	1171

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/558,149	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 January 2005 and 10 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-62,71-75 and 81-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60-62,71-75 and 81-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Compliance Form*.

DETAILED ACTION

The Group and/or Art Unit designation of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Valarie Bertoglio, Ph.D., Group Art Unit 1632.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/10/2005 has been entered.

Claims 1-59, 63-70 and 76-80 have been cancelled. Claims 60,61,62 and 71 have been amended. Claims 88-96 have been added. Claims 60-62,71-75 and 81-96 are pending and under consideration in the instant office action.

Priority

The priority statement at the first line of the specification should be updated to reflect the current status of the priority document. US Patent Application 09/059461 was allowed as US Patent No. 6,146,894, issued 11/14/2000.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent

Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The nucleic acid sequences notated in the specification require sequence identifiers. For example, see page 19 at lines 18,19,23,25,28 and 30.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Information Disclosure Sheet

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

The disclosure is objected to because of the following informalities:

The PMS2 5' primer sequence referred to at page 19, line 23 does not appear to correspond to the hPMS2 gene codons 1-6 as indicated. The wildtype PMS2 sequence at codons 1-6 is set forth in Genbank Accession # NM_000535 and in SEQ ID NO:1 as well as in Nicolaides et al (1998, **Mol. Cell. Biol.** 18:1635-1641, see page 1636, col. 1, last paragraph). It appears the primer sequence listed in the specification is in error.

Appropriate correction is required.

Double Patenting

Applicant is advised that should claim 81 be found allowable, claim 82 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Should claim 88 be found allowable, claim 89 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Should claim 92 be found allowable, claim 91 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The specification defines human PMS2-134 as having a truncation mutation at codon 134 (see page 7, lines 4-7) and therefore, the scope of each of claims 81 and 82, claims 88 and 89 and claim 91 and 92 are the same.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New matter

Claims 60-62 and 71-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claims 60-62 and 71 have been amended to recite "a PMS2-134 allele". Applicant points to the specification for support of these amendments at page 7, lines 13-23. However, page 7, lines 13-23 states only that dominant negative alleles of a mismatch repair gene can be obtained from cells of humans, animals, yeast, bacteria or other organisms. The specification at page 7, lines 13-23 does not specifically refer to or define PMS2-134. In fact, the specification does not make specific reference to PMS2-134 in any context other than referring to the known human allele (see page 7, lines 4-9). The specification only refers to non-human alleles in the general context of dominant negative alleles mismatch repair genes. There is no general description of the claimed genera of PMS2-134 genes or alleles. There is no structural or functional correlation between human PMS2 and other species of PMS2 that indicates that amino acid 134 has the same function in the various species such that the specifically claimed truncation will have the same dominant negative effect in each species. The specification describes only one species of PMS2-134 while the claims are directed to a genus of PMS2-134 alleles. For example, the only PMS2-134 allele described in the specification is that of the human gene. This limitation was omitted from the claim and is considered new matter as the use of any non-human species of PMS2-134 was not generically taught in the specification and therefore was not described in any way other than in the context of these other specifications.

Disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing.

See, for example, *In re Shokal*, 113 USPQ 283 (CCPA 1957); *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481 (CAFC 2000).

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

Enablement

The previous enablement rejection set forth at pages 2-4 of the office action dated 08/10/2004 is withdrawn in light of Applicant's arguments at pages 9-13 of Applicant's Remarks date 05/10/2005 demonstrating functional conservation between PMS2 mismatch repair genes of distantly related species. However, a new rejection is set forth below.

Claims 60-62,71-75 and 81-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose germ and somatic cells all comprise a transgene encoding a dominant negative human PMS2-134 gene product wherein

when the transgene is expressed the cells expressing the transgene exhibit hypermutability, does not reasonably provide enablement for the claimed mouse expressing any PMS2-134 gene or for the claimed mouse wherein the transgene is not expressed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims are drawn to a transgenic mouse (claims 60,61), methods of making a transgenic fertilized mouse egg (claim 62), wherein the somatic and germ cells of the mouse or the fertilized egg comprises an polynucleotide encoding a dominant negative PMS2-134 allele.

Claim 71 is drawn to a method of making the mouse using a fertilized mouse egg and testing the resultant mouse for mutations in a gene of interest. The independent claims encompass genes encoding PMS2-134 alleles other than the human gene taught by the specification. The claims broadly encompass the claimed transgenic mice or mouse eggs wherein the transgene is not expressed. Dependent claims 81-96 limit the PMS2 mismatch repair gene to human PMS2 but fail to require expression of the gene encoding human PMS2-134.

The specification has taught making isolated cells in vitro that express a recombinant gene encoding a dominant negative human PMS2-134 allele, the product of which is truncated after amino acid 133, wherein the cells are hypermutable as a result of the expression of the recombinant gene. To the extent that the specification has not described any other species of PMS2-134 gene that confers dominant negative activity (see rejections under 35 USC 112, 1st paragraph-New Matter and 35 USC 112, 2nd paragraph) the specification is not enabling for any species of PMS2-134 gene other human. The specification has prophetically taught making transgenic mice whose somatic and germ cells all comprise a transgene encoding a human PMS2-134 which is a mutant human gene comprising a truncation mutation at codon 134, resulting in a polypeptide with the N-terminal 133 amino acids. The specification has not taught that the PMS2 gene from a non-human species will have a dominant negative effect when truncated at amino acid 133. The specification does not teach or provide the means for determining that truncation of any PMS2 gene at amino acid 133 will result in proteins with the same function in mice. The specification does not provide PMS2 sequence from any other species to demonstrate any structural similarities in a way to allow determination of whether amino acid 133 from PMS2 of other species lies within the same functional domain. For

example, in the declaration by Nicholas Nicolaides dated 11/05/2003, it is shown that the PMS2 gene from human and Arabidopsis differ such that amino acid codon 134 of the two species do not align. In fact, it is codon 121 of Arabidopsis PMS2 that corresponds to, and would be expected to be equivalent functionally to, codon 134 of the human gene. Therefore, the specification fails to define any more than a single species of PMS2-134 gene and because one of skill in the art would not know what falls within the genus, one would not know what to make because the specification does not describe what it is.

The claims also fail to require that the transgene be expressed. The claims encompass mice or fertilized eggs whose genome comprises the claimed transgene but do not express it. It was well known in the art at the time of filing that transgenes inserted into the genome often shown variable expression or lack of expression depending on the site of integration. For example, Overbeek [1994, "Factors affecting transgenic animal production," **Transgenic animal technology**, pages 96-98] taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 **Theriogenology**, Vol. 45, pp. 57-68). Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome (Kappell, 1992, **Current Opinions in Biotechnology**, Vol. 3, pp. 548-553). The claims encompass mice

that fail to express the integrated transgene and the specification does not teach how to use such mice. As such, it would require undue experimentation to determine how to use the claimed mice that do not express the PMS2-134 gene in such a way as to cause hypermutability.

The claims do not require that the PMS2-134 allele be encoded by the transgene. The claims therefore encompass mice that comprise a PMS2-134 allele at the endogenous PMS2 locus. Use of the term "PMS2-134 allele", as set forth below under 35 USC 112, 2nd paragraph, infers that the dominant negative PMS2-134 gene is at the endogenous PMS2 locus in light of the art accepted definition of the term "allele" (see below). The specification does not teach such a mouse where the endogenous PMS2 gene has a dominant negative activity. Furthermore, dependent claims limiting the PMS2-134 allele to human PMS2-134 would not be enabled because the human PMS2 locus is not present in mouse. The specification only teaches a mouse whose genome comprises a transgene encoding a dominant negative human PMS2-134 gene. Claims should require that the dominant negative PMS2-134 be encoded by the transgene.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 60-62,71-75 and 81-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 60-62 and 71 are unclear because they refer to a genus of PMS2-134 dominant negative allele, which is an unclear reference in light of the teachings in the specification. The metes and bounds of the claimed genus of PMS2-134 genes are not clear. The specification teaches a single PMS2-134 truncation, that of the human gene. It is not clear whether the claim is intended to encompass PMS2 gene truncations from other species wherein the truncation is after codon 133 or is after the codon that aligns and corresponds to codon 133 of the human PMS2, which could be a different codon number, i.e. codon 121 of Arabidopsis according to Figure 1 of the Declaration submitted by Nicholas Nicolaides on 11/05/2003. Claims 72-75 depend from claim 71 and are included in this rejection.

Claims 60-62 and 71 are unclear because of the use of the term "allele". The specification fails to define the term "allele" and it is accepted in the art to refer to an alternative form of a gene located at a specific, designated genomic locus, (for example see the definition at http://216.251.232.159/semdweb/internetsomd/ASP/1487714.asp - attached). A locus is a defined endogenous chromosomal location that is not a characteristic of a randomly integrated transgene. Therefore, use of the term "PMS2-134 allele" is unclear because it is not known whether it is referring to a altered endogenous PMS2 gene at the PMS2 locus as would be interpreted in light of the art accepted definition of the term "allele" or if the claim is referring to a PMS2-134 transgene located at a genomic locus other than PMS2, as is taught by the specification. Claims 72-75, 91-93 and 96 depend from claim 71. Claims 81-83 and 95 depend from claim 62. Claims 84 and 88-90 depend from claim 60. Claims 85-87 and 94 depend from claim 61.

Claims 82,83,86,87,89,90,92 and 93 are unclear because claims 82,86,89 and 92 require that the mismatch repair gene comprise a truncation mutation as shown in SEQ ID NO:1 but SEQ ID NO:1 is a wild-type gene that is not truncated. As written, it is unclear whether the claims are referring to "...a truncation mutation...as shown in SEQ ID NO:1" or to "codon 134 as shown in SEQ ID NO:1". The truncation is not shown in SEQ ID NO:1. Suggested alternative claim language includes "...a truncation mutation at codon 134 of SEQ ID NO:1". Claims 83,87,90 and 93 depend from claims 82,86,89 and 92.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Application No.: 09/558149

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [ ] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

- [X] 7. Other: The nucleic acid sequences in the specification (see page 19) require sequence identifiers.

If Necessary, Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE